

While Applicants readily admit this attribute of Genbank classification, Applicants note that while the sequence comprising a gene may change over time, therefore altering the sequence associated with a particular accession number over time, the gross "identity" of that gene does not change. This makes it more appropriate, within the pattern concept of the present invention, to focus on the gene being identified, rather than the sequence itself, as the bit of information coded by the accession numbers set forth in the present specification.

Nonetheless, Applicants appreciate the Examiner's concern with respect even to identity, and therefore have amended the present specification to specify that an accession number, as used in the present specification, is understood to represent the identity of the gene so-specified as of the priority filing date of the present application. Hence, the rejection under § 112 has been overcome and reconsideration is respectfully requested.

35 U.S.C. § 102

Claims 1-6, 8, 9, 11-17, 20-22, 29 and 38-42 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kostulas et al., *Stroke* 29:462-466 (1998). Specifically, the Examiner asserts that Kostulas teaches a method of instant independent claims 1 and 38 of injury assessment in an individual because Kostulas teaches "the pattern of expression of the number of cells which express IL-8, MCP-1, MIP-1alpha, and MIP-1 beta as instant step (a), and comparison of the expression IL-8, as instant step (b). This rejection is traversed and reconsideration is respectfully requested.

Present claim 1 is directed to a method of injury assessment in an individual. The method comprises the steps of: a. determining a pattern of expression exhibited by blood cells obtained from the individual, and b.

55 comparing the pattern of expression exhibited by the obtained blood cells to an injury database to assess the injury, wherein the pattern of expression comprises patterns of gene expression, protein expression, or combinations thereof, and further wherein the injury database comprises organ specific injury database, disease specific injury database, or combinations thereof.

60 Present independent claim 38 is directed to a method of stroke injury assessment in an individual. The method comprises the steps of: a. obtaining a peripheral blood sample from the individual; b. capturing a pattern of expression; c. defining the pattern of expression; and d. comparing the pattern of expression to an injury database to assess stroke injury.

65 It is important to note that the term "pattern of expression," as employed by the Applicants, refers to a pattern derived from observation of expression across a database of genes, the database in the instant claims being comprised of multiple genes/molecules. The expression response profile of a single gene does not constitute the "expression pattern" according to the
70 present invention. For example, in the "Background of the Invention" section of the present specification, Applicants note that several investigators have determined specific gene responses induced by various injury states. Indeed, like Kostulas, Applicants note that Barone teaches the induction of interleukin-8 (IL-8), among other proteins, by brain stroke (page 3, third
75 paragraph).

On page 15 of the instant specification, Applicants define "pattern of expression" as referring to "the representation of molecules, including but not limited to genes, proteins or combinations thereof, in an injury state, which are upregulated, downregulated or embody no change." Significantly, Applicants specify exemplary "expression methods" intended to "define" a pattern of expression as "significance analysis" and "class prediction," both methods which deal with population levels of statistics, not an individual level. Further, Applicants note that the present specification at page 17 teaches that "at least 10" molecules are "necessary to define a pattern of expression." A pattern of expression is further depicted as being "captured" for a particular injury state (page 22, line 5).

Applicants point, in particular, to the present disclosure on pages 22 and 23 for an illustration of how to experimentally determine a pattern of expression. Note that such a determination requires, for example, ranking the molecules of a captured pattern of expression by, for example, assigning some ascending numerical value to the expression products, on the basis of their expression strength. Once a pattern of expression is captured and defined, the pattern of expression exhibited by an unknown blood cell sample may be compared to the injury database (page 25, bottom, bridging to the top of page 26).

Applicants note that both independent claims require comparison to an "injury database," which is defined on page 13 of the specification to refer to "a database comprising a pattern of expression or patterns of expressions indicative of a single or different states of injury. Applicants teach that such a

100 database is first established for a particular injury (page 22, line 6-9), by
capturing patterns of expression.

Hence, without the capture of a pattern of expression as required by
instant claims 1 and 38, and without generation of the injury database required
by instant claims 1 and 38, the present inventive methods cannot be practiced.

105 Kostulas, on the other hand, merely teaches the correlation of the
expression levels of the mRNA of a single protein, IL-8, "suggesting that IL-8
could be involved in recruiting blood PMNL to the sites of cerebral ischemia
(see Abstract, sentences beginning "Results" and "Conclusions"). Kostulas
fails to disclose any post-experimental processing of the levels derived, as
110 instantly required in order to capture and define the requisite "pattern of
expression" according to the present invention as set forth in present claims 1
and 38.

Further, Kostulas is investigating a potential role of IL-8 in "recruiting
blood PMNL to the sites of cerebral ischemia" (page 465, lines 6-7) for the
115 purpose of developing regiment to neutralize IL-8 in stroke victims (page 465,
column 2, lines 13-16). Kostulas does not teach or otherwise disclose the
generation of an injury database based on patterns of expression in order to
assess an injury.

Anticipation under 35 U.S.C. § 102(b) requires the disclosure in a
120 single prior art reference of each element of the claims under consideration,
Alco Standard Corp. v. TVA, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986).
Kostulas fails to disclose methods of injury assessment comprising, inter alia,
determining a pattern of expression and comparing the pattern of expression
exhibited to an injury database to assess the injury as required by the present

125 invention defined by instant independent claim 1. Nor does Kostulas teach or
disclose methods of stroke injury assessment according to instant independent
claim 38, which requires the steps of, inter alia, capturing a pattern of
expression, defining the pattern of expression, and comparing the pattern of
expression to an injury database, as defined by the present specification.

130 Hence, the rejection of claims 1 and 38, and claims 2-6, 8, 9, 11, 17, 20-22,
29, and 39-42 dependent therefrom, under 35 U.S.C. §102 under Kostulas has
been overcome. Reconsideration is therefore respectfully requested.

Claims 1-17, 20-22, and 29 are rejected under 35 U.S.C. § 102(e) as
being anticipated by U.S. Patent No. 6,316,197 to Das et al. ("Das").

135 Specifically, the Examiner asserts that Das teaches the methods of instant
independent claims 1 and 38 [it should be noted that instant claim 38 has not
been rejected on the basis of Das, so Applicants assume this mention is an
unintended artifact of it having been mentioned similarly in the prior rejection
basis], wherein the injury is exposure to a toxic agent. The Examiner further
140 asserts that Das teaches the pattern of gene expression of HCl and EIF-1,
where Das teaches that dozens of genes in peripheral blood are responsive to
SEP, which includes lipopolysaccharide, and to Anthrax, analysis of
peripheral blood samples, and "forms a pattern of expression," when
disclosing the observation that "the in vivo response reflected the pattern of
145 altered gene expression that we had seen in vitro." This rejection is traversed
and reconsideration is respectfully requested.

Instant claim 1 is set forth in detail, supra. In particular, Applicants
reiterate that the inventive method defined by claim 1 is a method of injury
assessment, and requires, inter alia, establishment of an injury database,

150 wherein the injury database comprises organ specific injury database, disease
 specific injury database, or combinations thereof.

 Das, on the other hand, discloses methods of diagnosing exposure to toxic
agents by taking samples of toxin-exposed and toxin-unexposed tissues from the same
individual, detecting an amount of protein/gene expression present in each,
155 determining the difference, and comparing this difference to a library of expected
 expression for pre-determined toxic agents (see, e.g. Abstract).

 Das, therefore, has a pre-determined database of toxins, based on
establishment of relative patterns of expression particular of a particular toxin.
Comparison of any generated pattern of expression, therefore, indicates,
160 theoretically, exposure to a particular toxin according to its alignment with one of the
 predetermined toxin databases. Applicants note also that Das teaches establishment
 of the toxin database by relative comparison, not by absolute generation, of patterns
 of expression. Importantly, Das is not assessing injury states by comparison to an
 injury database, but is assessing toxin identity by comparison to databases of toxins.

165 The present inventive method of assessing injury states, on the other hand,
 requires an injury data base, wherein the injury database comprises organ specific
 injury database, disease specific injury database, or combinations thereof. The
 comparison permits assessment of injury state, not exposure to and/or identity of a
 chemical compound, as allegedly permitted by the databases of Das.

170 As previously noted above, anticipation under 35 U.S.C. § 102(b) requires the
 disclosure in a single prior art reference of each element of the claims under
 consideration, *Alco Standard Corp.* 1 U.S.P.Q.2d 1337, at 1341. Das fails to teach an
 injury data base comprising either an organ specific database or a disease specific
 database, as required by instant independent claim 1. The sole database disclosed by

175 Das is a toxin database. Hence, the rejection under 35 U.S.C. §102(e) under Das has
been overcome and reconsideration is respectfully requested.

35 U.S.C. § 103

Claims 1-17, 20-22, 29 and 38-42 are rejected under 35 U.S.C. § 103(a) as
being unpatentable over Kostulas in view of U.S. Patent No. 6,040,138 to Lockhart et
180 al. ("Lockhart"). Specifically, the Examiner asserts that Kostulas teaches the methods
of independent claims 1 and 38 of injury assessment in an individual, as set forth in
the § 102 rejection, supra. The Examiner notes, however, that Kostulas fails to teach
elements of claims 7 and 10, and does not teach application of the method to
microarrays, which the Examiner asserts to be a "clear intent" of the present
185 invention, "though the limitation never currently appears in the claims." With respect
to the secondary reference, the Examiner asserts that Lockhart teaches a method of
analyzing expression of nucleic acids whose expression is altered in a disease state,
comprising the steps of (a) determining a pattern of expression using a microarray
exhibited by blood cells, and comparing the pattern to a database to assess injury .
190 The Examiner further asserts that Lockhart expressly teaches the steps of I) isolating
RNA from the cells, ii) preparing a labeled probe using the isolated RNA, iii)
applying the probe to a microarray, and iv) measuring the level of the RNA, allegedly
according to instant claim 7, expressly teaches labeling the cDNA product, according
to instant claim 10, and further teaches the use of chemokines like interleukin 6, a
195 glycosylated protein disclosed in instant Table 1, and as recited in instant claims 12-
15. The Examiner concludes that it therefore would have been prima facie obvious to
one of ordinary skill in the art at the time the invention was made to use the
microarray and microarray methods of Lockhart to analyze the gene expression in
stroke as discussed by Kostulas, since Lockhart notes "It will be appreciated that the

200 methods of this invention can be used to monitor the expression of any desired gene
of known sequence or subsequence...[and that] genes of particular interest for
expression monitoring include genes involved in the pathways associated with various
pathological conditions and whose expression is thus indicative of the pathological
condition," such that the ordinary practitioner, motivated by Kostulas to detect gene
205 expression in stroke, would have been strongly motivated to use the microarray
method of Lockhart to determine which genes were involved in stroke in order to
permit diagnosis as taught by Lockhart.

The recitations of independent claims 1 and 38 have been set forth in detail
above. In addition, in the analysis of the 102 rejection under Kostulas, Applicants
210 delineated the insufficiencies of the Kostulas disclosure with respect to the present
independent claims. That is, Kostulas fails to disclose or suggest methods of injury
assessment comprising, inter alia, determining a pattern of expression and comparing
the pattern of expression exhibited to an injury database to assess the injury, as
required by the present invention defined by instant independent claim 1.

215 As noted in the prior traversal, Kostulas does not use the term "expression
pattern" in a manner that comports with the term "pattern of expression," as instantly
defined by the specification. Nor does Kostulas teach or disclose methods of stroke
injury assessment according to instant independent claim 38, which requires the steps
of, inter alia, capturing a pattern of expression, defining the pattern of expression, and
220 comparing the pattern of expression to an injury database, as defined by the present
specification.

The secondary reference, Lockhart, is directed to methods of analyzing the
expression of one or more genes (see, e.g. claim 1, and Abstract). While Applicants
agree that Lockhart discloses subject matter that permits simultaneously monitoring

225 the expression of a multiplicity of genes, and touts the method as effective for
monitoring gene expression "involving pathways associated with various pathological
conditions (column 4, lines 64-67), Applicants submit that Lockhart does not teach or
suggest the present methods of assessing an injury state, and does not overcome the
deficiencies of the primary reference with respect to teaching or disclosing, inter alia,
230 determining and defining a "pattern of expression" according to the present invention,
or an injury database derived from determining and defining such patterns of
expression for specific injury states, wherein the injury database comprises organ
specific injury database, disease specific injury database, or combinations thereof.

To establish prima facie obviousness of the claimed invention, all the claim
235 limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981,
180 U.S.P.Q. 580 (CCPA 1974). The deficiencies of Kostulas are set forth in detail,
supra. Kostulas fails to teach or suggest, inter alia, "patterns of expression" defined
according to the present invention, or injury databases, wherein the injury database
comprises organ specific injury database or disease specific injury database, or
240 combinations thereof, and fails to disclose, specifically, an injury database for stroke
injury as required by instant claim 38. The secondary reference fails to address or
overcome these deficiencies. Hence, a prima facie case has not been established and
the rejection of claims 1 and 38, and the claims dependent therefrom has been
overcome. Reconsideration is therefore respectfully requested.

245 Applicants believe that the above represents a complete and effective response
to the rejections of the present claims under 35 U.S.C. §§ 112, 102, and 103. Hence,
reconsideration and an early allowance are respectfully requested.

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